Wiltshire SP4 OJG, United Kingdom on 6 February 1995] under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

7. (AMENDED) A specific [binding substance] monoclonal antibody [including] comprising an immunoglobulin antigen binding domain [obtainable] obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), [Centre for Applied Microbiology & Research, Salisbury, Wiltshire SP4 OJG, United Kingdom on 6 February 6, 1995] under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

8. (AMENDED) A specific [binding substance] monoclonal antibody which competes for binding to cervical tissue with a [specific binding substance] monoclonal antibody according to claim 7.

Remarks

Claims 6 and 9 have been cancelled. Claims 1-5 and 7-8 have been amended and are pending. Support for the amendments is found in the claims as filed and throughout the specification, for example at page 20, lines 15-17, at page 25, lines 26-28 through page 26, lines 1-2, and at page 47, lines 12-15.

Claim Objections

Claims 1-9 are objected to for lacking proper introduction. An amendment is included herein to correct the introduction.

Claims 3, 5, and 7 are objected to for inclusion of date and address information. The claims are amended to delete the aforesaid information.

Specification

The specification is objected to for lacking an abstract. An abstract has been inserted at new page 59.

The specification has been amended to correct all citations of "TEXAS RED® ."

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. With regard to the rejection of Claims 3, 6, and 7 for the recitation of "immunoglobulin antigen binding domain obtainable" (Paper No. 7, page 4, 3rd paragraph), Applicants submit that the claims are not indefinite because the specification cites methods for obtaining the antigen binding domain from a hybridoma. For example, at page 11, lines 8-19, Applicants describe isolation of nucleic acid encoding monoclonal antibodies, and at page 5, lines 11-16 recite methods for identifying the antigen recognized by antibodies or fragments thereof. (*See also* page 9, lines 5-11). Thus, the rejection with regard to these claims should be withdrawn.

Applicants submit that with regard to all other rejections the claims as amended are now in condition for allowance. Thus, the remaining rejections should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-9 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of determining changes in cells of the cervix indicative of a premalignant or neoplastic condition or disease comprising determining binding of specific monoclonal antibodies to the cells in a sample and comparing the pattern of binding in normal cervical cells, does not reasonably provide enablement for a method of determining any abnormality in a tissue sample containing cells of the cervix. The claims as amended recite a method which is clearly enabled by the specification. Applicants respectfully submit that the rejection should be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as being anticipated by any of Kerr et al. (UK 2 215 046 (1989), "Kerr"), Porta et al. (*Pat. Clin. Ost. Gin.*, 14:348-55 (1986), "Porta"), Kamiya et al. (*Acta Cytologica*, 37:131-34 (1993), "Kamiya"), or Smedts et al. (*Amer. J. Pathol.*, 142:403-12 (1993), "Smedts").

Kerr teaches a method of grading cervical intraepithelial neoplasia (CIN) by treating cervical tissue with neuraminidase, staining with a CD15 monoclonal antibody, comparing staining in normal tissue and dysplastic tissue, and classifying the extent of staining to provide an indication of the grade of CIN present.

Porta generally teaches the use of monoclonal antibodies in immunohistological techniques as a means of identifying abnormal patterns of antigen expression in neoplastic cervical epithelium for diagnosis and prognosis.

Kamiya teaches detection of cervical small cell undifferentiated carcinoma comprising staining samples of cervical cells with monoclonal antibodies against cluster 1 small cell lung cancer antigen and comparing the staining pattern to non-small cell cervical cancers.

Smedts teaches determination of cervical neoplasia and carcinoma comprising determining the binding of monoclonal antibodies directed against specific keratins with samples of cervical cells and comparing the pattern of expression of the keratins in the sample with the patterns of expression in normal and malignant cells.

Claim 1, as amended, is directed to a method for determining a premalignant or neoplastic disease state in a cervical tissue sample. The method comprises contacting two or more monoclonal antibodies with said tissue sample, determining binding of the monoclonal antibodies to the sample, and comparing binding with a binding pattern on a normal cervical tissue sample. The monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells.

"Anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference... There must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of invention." Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001.

Kerr, Porta, Kamiya and Smedts do not teach the method comprising two or more monoclonal antibodies with a tissue sample. Since the references do not teach each and every limitation of Claim 1, they do not anticipate Claim 1 under 35 U.S.C. § 102. Applicants respectfully request the Examiner to withdraw this rejection.

Rejections under 35 U.S.C. § 102/103

Claims 4 and 8 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over any of Kerr, Porta, Kamiya, or Smedts.

Kerr, Porta, Kamiya and Smedts are discussed above. The Examiner states that "because any of the cited references teach monoclonal antibodies which bind to the cells in the sample, in sufficient quantities these monoclonal antibodies would inherently interfere or compete with the binding of other monoclonal antibodies due to stearic hindrance" (Paper No. 7, page 11, 1st paragraph). The Examiner's rejection appears to rely on the possibility that antibodies taught in the prior art may, in sufficient quantities, compete for binding with the specifically recited monoclonal antibodies of the invention.

Applicants respectfully traverse. Claims 4 and 8 recite specific antibodies and a method using specific antibodies wherein the specific antibodies compete for binding for any one of the specifically recited monoclonal antibodies. The Examiner appears to be referring to non-specific binding interactions and not binding via a specific, competitive interaction, which the claims recite. Antibodies that bind through non-specific binding mechanisms are not encompassed by the claims, due to the terms "compete" and "specific."

Anticipation under 35 U.S.C. § 102, as discussed above, requires that all elements of a claim be taught in a single art reference. None of the cited references discusses antibodies that specifically compete with the specific monoclonal antibodies of the claims. Therefore, the rejection under 35 U.S.C. § 102 should be withdrawn.

With regard to the rejection of Claims 4 and 8 under 35 U.S.C. § 103, there are three requirements to establish a *prima facie* case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the

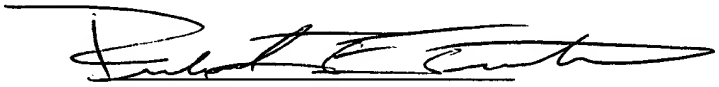
knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations" (MPEP § 2143).

Applicants submit that none of the three requirements for a showing of obviousness has been satisfied. First, there is no suggestion or motivation in any of the cited references to modify or combine references to obtain the claimed invention. Second, there is no reasonable expectation of success that one could arrive at the present invention by combining the cited references. Third, the references do not teach all of the claim limitations. For example, the references do not teach the specific antibodies of the invention, nor do they teach specific antibodies that compete for binding with the specific monoclonal antibodies of the invention. Thus, a *prima facie* case has not been met. Applicants respectfully submit that the rejection based on obviousness be withdrawn.

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP



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APPENDIX OF CLAIMS:

1. (AMENDED) A method of determining a premalignant or neoplastic disease state in a tissue sample containing cells of the cervix, the method comprising contacting a panel of two or more monoclonal antibodies with said tissue sample, determining binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding of said monoclonal antibodies to a normal cervical cell sample, wherein said monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells.

2. (AMENDED) A method according to claim 1 wherein the monoclonal antibodies comprise one or more polypeptides each comprising an antigen binding domain.

3. (AMENDED) A method of determining a premalignant or neoplastic disease state in a tissue sample containing cells of the cervix, the method comprising contacting one or more monoclonal antibodies with said tissue sample, determining binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding of said monoclonal antibodies to a normal cervical cell sample, wherein said monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells and wherein the monoclonal antibodies comprise one or more polypeptides each comprising an antigen binding domain obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

4. (TWICE AMENDED) A method according to claim 1 wherein the monoclonal antibodies comprise one or more monoclonal antibodies which specifically compete for binding to cervical tissue with one or more antibodies obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

5. (AMENDED) A hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

7. (AMENDED) A specific monoclonal antibody comprising an immunoglobulin antigen binding domain obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

8. (AMENDED) A specific monoclonal antibody which competes for binding to cervical tissue with a monoclonal antibody according to claim 7.